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In vitro activity of linezolid and eperezolid against anaerobic bacteria

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Linezolid (PNU-100766) and eperezolid (PNU-100592) belong to a new class of synthetic antimicrobial agents called the oxazolidinones [1]. These agents are highly active against many clinically important Gram-positive bacteria including methicillin-resistant staphylococci, vancomycin-resistant enterococci and penicillin-resistant pneumococci with MIC_{90} values usually ranging from 0.5 to 4 mg/L [2,3]. Gram-negative aerobic microorganisms are generally not inhibited by these compounds. The oxazolidinones exhibit a unique mechanism of bacterial protein synthesis inhibition, resulting in mainly bacteriostatic activity [1].

Anaerobic bacteria are a common cause of serious infections. The anaerobic species which predominate in clinical infections include the *Bacteroides fragilis* group, *Clostridium* spp., *Fusobacterium nucleatum* and *Peptostreptococcus* spp. Treatment of anaerobic infections is often difficult, since many anaerobes are intrinsically resistant to certain antimicrobial agents such as aminoglycosides, trimethoprim, sulfamethoxazole, most quinolones and monobactams [4]. Resistance against tetracyclines is widespread, and many clinically important anaerobes exhibit resistance against clindamycin and several β-lactam agents. Resistance against cefoxitin, imipenem and metronidazole has been reported, although it is uncommon. Drugs commonly used in the treatment of anaerobic infections are β-lactam compounds, clindamycin, metronidazole and chloramphenicol [5].

The aim of the present study was to determine the in vitro activity of linezolid and eperezolid against 360 anaerobic bacterial strains isolated from human infections.

Three hundred and sixty anaerobic clinical isolates, including *Peptostreptococcus* spp. (50 strains), *Propionibacterium acnes* (30 strains), *Clostridium perfringens* (30 strains), *C. difficile* (50 strains), *B. fragilis* (50 strains), *Bacteroides, Porphyromonas,* and *Prevotella* spp. (100 strains) and fusobacteria (50 strains), collected at the Huddinge University Hospital, Stockholm, Sweden were tested. All strains were identified by biochemical tests and gas–liquid chromatographic analyses of metabolic end products according to the techniques described by Summanen et al. [6]. The strains were cultured in prereduced yeast glucose medium or in prereduced chopped meat broth with glucose. Linezolid and eperezolid were obtained from Pharmacia & Upjohn Inc., Kalamazoo, MI, USA. Fresh dilutions of each compound were prepared daily. The antimicrobial agents were suspended and diluted according to the manufacturers' instructions. Antimicrobial susceptibility tests were performed by the agar dilution method using PDM-ASM agar (Biodisk, Stockholm, Sweden), with the addition of 5% defibrinated horse blood. Antimicrobial concentrations from 0.008 to 128 mg/L were obtained by incorporation of each substance when preparing the agar plates. The inocula consisted of 48-h broth cultures diluted in prereduced yeast glucose medium to a final inoculum of 10^8 CFU/mL. Then, 1.0–2.0 μL was applied to the agar plates with a modified Steers replicator, resulting in approximately 10^3 CFU per spot. An agar plate without antimicrobial agent was always included as growth control. Agar plates were incubated in anaerobic jars (GasPak, BBL, Microbiology Systems, Cockeysville, MD, USA) for 48 h at 37°C. The MIC was defined as the lowest concentration that inhibited growth of organisms on the agar plates. A barely visible haze or the appearance of a single colony was disregarded. Three control strains were used to monitor the antimicrobial susceptibility test: *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741 and *C. perfringens* ATCC 13124.

Ninety per cent of all tested *Peptostreptococccus* spp. (50 strains), *Propionibacterium acnes* (30 strains), *C. perfringens* (50 strains) and *C. difficile* (50 strains) were inhibited by ≤2 mg/L linezolid and eperezolid.

Table 1 In vitro activity of linezolid and eperezolid against 360 anaerobic bacterial strains

Microorganism (no. of isolates tested) and antimicrobial agent	MIC (mg/L)		
	Range	MIC_{50}	MIC_{90}
Peptostreptococcus (50)			
Linezolid	0.25–2.0	1.0	2.0
Eperezolid	0.25–1.0	0.5	1.0
Propionibacterium acnes (30)			
Linezolid	0.25–1.0	0.5	0.5
Eperezolid	0.5–1.0	0.5	1.0
Clostridium perfringens (50)			
Linezolid	1.0–4.0	2.0	2.0
Eperezolid	1.0–2.0	2.0	2.0
Clostridium difficile (50)			
Linezolid	1.0–2.0	1.0	2.0
Eperezolid	0.5–1.0	1.0	1.0
Bacteroides fragilis (100)			
Linezolid	2.0–4.0	4.0	4.0
Eperezolid	2.0–32	8.0	16.0
Bacteroides, Porphyromonas, Prevotella (50)			
Linezolid	0.25–8.0	2.0	4.0
Eperezolid	0.125–8.0	2.0	8.0
Fusobacterium (30)			
Linezolid	0.25–8.0	0.5	8.0
Eperezolid	0.125–2.0	0.25	2.0

Linezolid showed higher activity (MIC_{90} 4.0 mg/L) against *B. fragilis* (100 strains) compared to eperezolid (MIC_{90} 16 mg/L). The MIC values (range, MIC_{50} and MIC_{90}) for the 360 tested strains of linezolid and eperezolid are shown in Table 1. Strains with intrinsic resistance to conventional anti-anaerobe agents, including three *C. difficile* strains and one *B. fragilis* strain resistant to clindamycin, seven *B. fragilis* strains resistant to cefoxitin, and one *B. splanchnicus* resistant to metronidazole, did not show any cross-resistance to the oxazolidinones.

The results of the present study are in accordance with previous reports on in vitro susceptibility to linezolid and eperezolid of anaerobic microorganisms [3]. Oral administration of linezolid (400 mg PO) and eperezolid (1000 mg PO) to healthy volunteers has earlier been reported to yield peak serum concentrations of 12.38 mg/L and 6.28 mg/L, respectively, while the trough concentrations were estimated to be 7.9 mg/L and 1.62 mg/L, respectively [7]. These serum levels of linezolid are well in excess of the MICs for anaerobic Gram-positive bacteria as well as for many anaerobic Gram-negative microorganisms. Concerning eperezolid, anaerobic Gram-positive bacteria are mainly susceptible to achieved serum levels. Linezolid has been reported to be active versus experimental *B. fragilis* soft tissue infections in mice [8]. Future clinical studies will show the potential of the oxazolidinones in the treatment of anaerobic infections. In conclusion, the new oxazolidinones linezolid and eperezolid have excellent activity against Gram-positive anaerobic microorganisms, with linezolid also exhibiting activity against *Bacteroides* spp. These agents may be useful in the treatment and prophylaxis of anaerobic infections.

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Identification of methicillin-resistant *Staphylococcus aureus* by latex agglutination kits: performance with epidemic strains (EMRSA) and strains causing problems with latex agglutination methods

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Agglutination kits for the identification of *Staphylococcus aureus* have been available for a number of years as an alternative to the coagulase test. The tube coagulase test, which detects the production of free coagulase, was considered to be the standard (sensitivity 95–98%) but it takes 4–24 h for completion [1,2]. A more simple